

Remarks

This Amendment is in response to the Office Action dated **November 21, 2007** in which claims 2-12, 29, 30 and 33-40 have been rejected. The rejections are traversed. Reconsideration is requested.

Claims 2-12, 29, 30 and 33-44 are currently pending in the application.

I. Claim Rejections - 35 U.S.C. § 102 - Anticipation Rejection and Compliance With 37 CFR 1.111(b)

Claims 2-6, 8-9, 11-12, 29-30 and 33-40 have been rejected as anticipated by *Beachy et al*, US 6,432,970 (*Beachy et al*'970). The rejections are traversed. *Beachy et al*'970 does not anticipate any of claims 33, 37, 39 or 40. Hence, *Beachy et al*'970 does not anticipate the invention of any of the currently pending claims.

The factual determination of anticipation requires the disclosure of each and every element of the claimed invention in a prior art document or else the claimed invention must be inherently present in prior art. Reliance on inherency in an anticipation analysis requires evidence that the missing descriptive matter is "necessarily present" in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. MPEP §2131.01 (III); *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). ***Inherency may not be established by probabilities or possibilities.*** The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *Continental Can*, 948 F.2d at 1269, 20 USPQ2d at 1749; *In re Robertson*, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999).

To be declared anticipating, a prior art document must also enable the invention. Mere

naming of a subject matter is insufficient for enablement, if the claimed invention cannot be made without undue experimentation. Determination of enablement must be made by taking the evidence as a whole, in particular when the teachings in a document are self-contradicting and ambiguous. Also, when a patent has teachings that are inoperative in entire categories of the teachings, undue experimentation is required to distinguish inoperative embodiments from those that are operative and consequently there is a clear failure of enablement. This principle is ancient and well established in the law of anticipation. See *In re Brown*, 141 USPQ 245, 249 (CCPA 1964) and the quotation therein from I Robinson on Patents 451 (1890).

More recent cases recognizing and applying the rule of enablement to the question anticipation include *In re Donohue*, 766 F.2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985); *Akzo N.V. v. United States Int'l Trade Commission*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986); *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299, 1304 (Fed. Cir. 2000); and *Elan Pharmaceuticals, Inc. v. Mayo Foundation*, 346 F.3d 1051, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

A. *Beachy et al '970* - Column 44, Lines 26-29 - Dosage

Teachings of *Beachy et al '970* were analyzed in the 6/11/2007 Amendment filed in this application (see page 6 to page 17). Explanations and facts were presented demonstrating that the presently described and claimed invention was neither anticipated nor inherently present in prior art.

The opinion is expressed in the Office Communication that Applicant's arguments have not shown the language of pending claims to be distinguishable from the teachings in prior art and that they fail to comply with 37 CFR §1.111(b). Office Communication declares that claims 2-6, 8-9, 11- 12, 29-30 and 33-40 stand rejected for being anticipated by *Beachy et al '970*.

Specifically, it is stated that *Beachy et al '970* had taught in prior art a dose range from about 0.0001 to about 100 mg per kilogram of body weight per day for compounds of invention and that Applicant has not provided evidence that what was previously taught in terms of dosage will not produce what is claimed in the present application. Applicant disagrees respectfully and points out to the following.

The quotation in the Office Communication from *Beachy et al '970* concerning dosage is misleadingly incomplete. Teachings in a prior art document must be considered as a whole. Whereas without a guidance the skilled person would have faced a task of evaluating every conceivable dose within a range covering one million-fold difference between the lowest and highest ends, *Beachy et al '970* specifically teaches in the passages immediately preceding the quoted passage that a minimal dose of a subject compound is to be used in the subject method to obtain a therapeutic effect described therein (“*start doses ...at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase until the desired effect is achieved... a suitable daily dose ...will be that... is the lowest dose effective to produce a therapeutic effect*”; see column 44, lines 14-24). The therapeutic effect to be achieved, as far as it can be derived unambiguously from the whole of *Beachy et al '970*, is the causation of an inhibition of cell proliferation in association with the inhibition of Hh/Smo signaling (see the 6/11/2007 Amendment). Inhibition of cell proliferation is also the effect described with a Hh antagonist in the experiments cited in *Beachy et al '970* to support the teaching that subject method employing a subject Hh antagonist can be used to treat cancer and other “proliferative disorders” (“...Sonic hedgehog stimulates the incorporation of BrdU into carcinoma cells ... while anti-Shh-N inhibited...therefore...the subject method can be used as part of a treatment of lung carcinoma”; emphasis added; see column 35, lines 46-59). Also, what is contemplated in

Beachy et al'970 as a therapeutic effect, specifically in the treatment of cancer, is the causation of an inhibition of proliferation of cancer cells (“... *pharmaceutical preparations of the invention are intended for the treatment of hyperplastic...as well as...neoplastic epidermal conditions such as those characterized by a high proliferation rate for various skin cancers*”; column 41, lines 25-31). The claims are also directed to the administration of a compound that is said to inhibit Hh/Smo signaling to a patient having “a *hyperproliferative disorder*” including cancer (see claims 1, 3-6, 14-16). It is clear that a skilled person who is following the teachings of *Beachy et al'970* will stop administration of a subject medicament when he/she observes inhibition of proliferation. He/she is specifically taught not to exceed the lowest dose effective. All that the 0.0001 to about 100 mg per kilogram of body range teaches is that a skilled person can expect to find such dosage somewhere in that million-fold range, not that a treatment with any dosage in the range will be safe or effective.

Nothing in *Beachy et al'970*, or in the entire prior art, leads a skilled person to expect that administration of a dosage that far exceeds the minimum dosage required to produce inhibition of proliferation could be used to cause highly selective and efficient differentiation and apoptosis of tumor cells *in vivo* to produce shrinking and disappearance of a tumor while sparing normal cells. To the contrary, the unambiguous and supported teachings in *Beachy et al'970* are teaching away, similar with the entire prior art. Thus, the *actual experimental findings described in Beachy et al'970 concerning the effect of sufficient concentrations of Hh antagonists on differentiation outcome of target cells is the inhibition of differentiation* (see e.g. the exemplifications; column 57, line 33 to column 63, line 29).

Beachy et al'970 directly teaches further away from the presently claimed invention by making a generalized teaching in reference to the well known requirement of cellular

proliferation for causation of cell death by radiation and other prior art non-surgical cancer treatments. It is taught explicitly that a *Hh antagonist used in the subject method will often provide a cytostatic effect and therefore the subject method can be used to inhibit programmed cell death* by providing an inhibition of proliferation (see column 40, line 57 to column 41, line 5).

The rest of the prior art, on the basis of experimental investigations, was also teaching directly away from considering to use a specific inhibitor of Hh/Smo signaling for causation of death of tumor cells in a patient (see the 6/11/2007 Amendment, the 1/10/2007 Amendment and the attached Declaration, Table III). The skilled person is well acquainted with the serious problems of non-surgical tumor treatments resulting from causation of damage to normal stem cells and he/she would be particularly discouraged to exceed a minimal dose effective to inhibit tumor cell proliferation, taking note that normal stem cells have been described to be absolutely dependent on Hh/Smo signaling (*Zhang Y et al, Nature* 2001; 410: 599-604; filed with the 1/10/2007 Amendment).

Unlike the situation in the prior art, the present application demonstrates, and numerous post-published investigations have independently confirmed, that a specific inhibitor of Hh/Smo signaling can be used to obtain the presently claimed technical effects on tumor cells and in a tumor-bearing subject. However, aiming for a minimal dose that is effective to inhibit proliferation of the tumor cells clearly fails to provide the presently claimed technical effects and treatment results (see the 1/10/2007 Amendment, the Declaration attached thereto, the 6/11/2007 Amendment and the scientific publications cited and filed therewith). Thus, for more than one reason, a skilled person following the teachings in *Beachy et al '970* would not be able to reach to

the presently claimed invention and the language of present is distinguished from the teachings in prior art, including *Beachy et al '970*.

B. *Beachy et al '970*, is non-enabling except for the exemplified subject matter, it is inoperative and without credibility in entire categories of teachings and it requires undue experimentation.

Beachy et al '970 does not anticipate the presently described and claimed invention for further reasons as well.

Beachy et al '970 discloses an unlimited number of compounds on the one hand and discloses on the other hand a long list of highly heterogenous conditions (including conditions that are poorly defined/undefined) as conditions that can be treated by administering a subject compound (see column 8, line 38 to column 11, line 67 and column 29, line 33 to column 42, line 56), encompassing almost every known pathological condition as a condition that can be treated by the “subject method” (which mainly boils down to the administration of a Hh antagonist). This is not credible without explicit demonstration. Applicant is not merely taking issue with what the Office Communication calls the “breadth” of the description, but rather of its fantastical character.¹ It seems a wonder what a “subject method” will do in “prophylaxis, therapy and cure” (column 44, lines 34-35) of so many maladies on which physicians and patients have been struggling from time immemorial and even in case of conditions affecting mankind universally (see column 33, lines 2-3)! To demonstrate this apparently wondrous “subject method,” however, not a single working example is provided for even one of the listed maladies. Mere enlistment of a condition as being treatable by a method, without supporting evidence in a prior art document, or in the rest of prior art, does not amount to enablement.

¹ To illustrate the fantastical character of the assertions in *Beachy et al '970* regarding the “subject method,” some of the statements have been extracted from *Beachy et al '970* and are listed in Appendix A, attached.

Even if a skilled person considers that some of the enlisted uses might be operative, he/she must carry out an undue amount of experimentation just to determine which teachings therein are operative and which ones are inoperative. The teachings are clearly inoperative in entire categories of the conditions taught to be treated by administering a subject Hh antagonist (see the 6/11/2007 Amendment).

As has been shown previously (see the 6/11/2007 Amendment), and as developed further herein, the *Beachy et al '970* teachings that are based on the experimental findings (described therein or in the scientific publications cited therein), directly teach away from contemplating to use a subject Hh antagonist to induce differentiation and/or apoptosis of tumor cells.

On the other hand the statements in *Beachy et al '970* that are not based on such experimental findings are typically ambiguous and self-contradictory regarding the expected effect of the subject method on the differentiation outcome and/or survival of target cells. Thus, the subject method employing a subject Hh antagonist can be used to “change” or “manipulate” or “modulate” the state of differentiation and/or survival of a cell according to *Beachy et al '970* (see the 6/11/2007 Amendment for examples quoted from *Beachy et al '970*). Such unsupported disclosures in *Beachy et al '970* are in addition directly self-contradicting concerning the expected effect on cell survival and cell differentiation (see column 33, lines 23-26 and column 34, lines 39- 42, 55-58; see also column 39, lines 10-15 and column 41, lines 47-51). The teaching is self-contradictory even when it is considered for epithelial cells alone or for a particular epithelial cell type (epidermal cells). Still further, when a disease has been selected, on what particular cells in the patient is an effect to be achieved and how? It is well known that diseased tissues contain many different cell types that are proliferating. It is also known that different cell types in an organism can respond even in the opposite directions in terms of

proliferation following administration of a specific inhibitor of Hh signaling (see e.g. vandenBrink GR et al 2001 filed with the 3/9/2006 RCE with Amendment).

To derive the invention from *Beachy et al '970* the skilled person must select a specific condition from a list too fantastical to believe, select particular compounds from a very wide range of compounds that includes those that are not within the language of the claims (see e.g. col. 33, lines 56-61), produce an effect that clearly is not necessarily required in anything expressly taught in *Beachy et al '970* and has not been reported previously, and do so by selecting a dosage against the wisdom in the art and from within a million-fold range that violates other specific teachings limiting the dosage selection. If this is not undue experimentation, nothing is.

C. *Beachy et al '970* - Other Disclosures Quoted in the Office Communication

The other disclosures quoted in the Office Communication from *Beachy et al '970* are also inadequate to support the anticipation rejection.

1. Column 9, lines 8-14

The Office Communication refers to the disclosures in column 9, lines 8-14 of *Beachy et al '970* to state that *Beachy et al '970* has teachings that are specific with respect to the therapeutic effects that may be achieved. The quoted disclosure states that “An effective amount of...a hedgehog antagonist...refers to an amount... which...brings about **a change** in the rate of cell proliferation and/or the state of differentiation of a cell and/or rate of survival of a cell according to the clinically acceptable standards for the disorder to be treated” (emphasis added). Since a “change” includes the precise opposite effects of the promotion and inhibition, there is no specificity in said teaching with respect to the effects to be achieved. Qualifying the change to

be in accord with “clinically acceptable standards for the disorder to be treated” does not amount to a specificity sufficient to avoid undue experimentation. It is illustrative to look at the particular example of what were considered in prior art clinically acceptable in tumor treatment. Causation of damage to the normal cells (particularly the stem cells and progenitor cells) is a well-known, nearly universal or “standard” effect of prior art chemotherapy/radiotherapy protocols for cancer, resulting in such unwanted early effects like the falling of hair and anemia in patients. Even when a patient and treating physician is willing to accept these standard effects of prior art treatments, it has been well known with many tumors that causation of tumor disappearance is *not* a standard outcome to be expected. None of the results obtained with the present invention, as recited in each of the pending independent claims are in accord with the prior art “standard” effects or results for tumor treatment.

Whereas the disclosure quoted from column 9, lines 8-14 of *Beachy et al'970* lack specificity concerning the therapeutic effects that may be achieved by administering an effective amount of a Hh antagonist, teachings are found elsewhere in the same document that are specific concerning the effects to be achieved with an effective amount of a Hh antagonist. For example, with respect to the effects on cellular differentiation, experimental findings are described showing that applying sufficiently high amounts of a subject Hh antagonist will consistently cause an *inhibition* of differentiation effect (column 58, lines 5-19), i.e. the *opposite* of inducing differentiation. It is a change in the "state of differentiation," but not one that is called for in any of the claims presented herein. Thus it is clear from the foregoing that the teachings quoted in the Office Communication from *Beachy et al'970*, column 9, lines 8-14 do not *necessarily* describe the present invention and so cannot make said document anticipating. Likewise, the statement quoted from column 29, lines 34-38, (“*modulating* a differentiated state, survival

and/or proliferation of a cell responsive to a hedgehog protein...as the circumstances may warrant”) is lacking enablement or utility as to the presently claimed invention. Because a differentiated state, survival and/or proliferation of a cell can be *modulated* in the way of promotion or inhibition and since these are the precise opposite of each other, there is no specificity in said teaching and it cannot be said to *necessarily* teach an effect as recited in the present claims.

2. Column 45, lines 9-17

The teaching quoted in the Office Communication from *Beachy et al* '970 stating that “therapeutically-effective amount of...a compound of the present invention...is effective for producing some desired therapeutic effect by inhibiting a hedgehog signaling pathway...and thereby blocking the biological consequences of that pathway” likewise has also no enablement or utility to a skilled person in art. Not only is there a lack of description of specifically what biological consequences are to be expected in what particular cells or tissues but it has been independently described in several scientific publications that an amount of a Hh antagonist effective producing inhibition of Hh signaling in particular cells in an animal will not *necessarily* be effective to produce, *e.g.* an inhibition of proliferation effect or an induction of apoptosis effect in them (see the 7/10/2007 Amendment, the attached Declaration, the 6/11/2007 Amendment and the scientific publications filed therewith). Further relevant is the fact that consequences of a systemically administered Hh antagonist on different cell types in an animal can be very different (even in the opposite directions), *e.g.* concerning cell proliferation (see the 3/9/2006 RCE with Amendment, *e.g.* the *van den Brink GR et al* 2001 publication filed therewith). Thus, the quoted statements from *Beachy et al* '970, column 45, lines 9-17 likewise do not constitute a teaching that makes present claims anticipated.

3. Column 33, lines 21-26

The Office Communication refers to *Beachy et al'970*, column 33, lines 24-26 to state that presently claimed invention is anticipated. The referred passage in *Beachy et al'970* states that “hedgehog antagonists can be utilized to cause such transformed cells to become either post-mitotic or apoptotic.” This statement is made without any experimental support and directly contradicts other teachings in *Beachy et al'970* as already pointed out. A skilled artisan presented with *Beachy et al'970* considers it as a whole, taking into account the fantastic character of the disclosed utilities that are lacking supporting evidence, and applying his/her general knowledge in art that pertains. In particular, the skilled artisan would take notice of the following.

i) The quoted passage states that transformed cells may become either post-mitotic *or* apoptotic. Thus a skilled artisan might arrive either at cells that are post-mitotic or at cells that are apoptotic, without necessarily achieving both. Accordingly, *by its own terms* apoptotic cells are not *necessarily* a result of the embodiment of the subject method being referred to.² Further, there is no way of learning from *Beachy et al'970* under what conditions a skilled artisan might arrive at apoptotic cells versus post-mitotic cells. This requires undue experimentation as already discussed. Hence it is not possible to say that the quoted passage of *Beachy et al'970* is a specific or enabling teaching for obtaining apoptosis of transformed cells.

ii) *Beachy et al '970* makes a generalized teaching elsewhere to state that a hedgehog antagonist will often have an inhibition of proliferation effect on epithelial cells and that

² As a matter of law therefore this is not an anticipation. See cases cited on page 6, above.

it will not have a cell killing effect (see column 40, line 57 to column 41, line 5). This a generalized teaching: “Moreover, because a *hedgehog antagonist will often be cytostatic to epithelial cells*, rather than cytotoxic...” Although the application of this teaching is not explicitly applied to cancer treatments there is no restriction of this teaching to a particular epithelial cell type. It is well known in art that most cancers originate from epithelial cells (*e.g.* the ependymomas mentioned on col. 33, lines 28-29 of *Beachy et al '970*) and *Beachy et al '970* also indicate nearby this teaching that a hedgehog antagonist can be used in treatment of “neoplastic *epidermal* conditions such as those characterized by a high *proliferation rate*” (column 41, lines 25-30 emphasis added). Therefore the skilled person expects that at least for most cancers, when the neoplastic or transformed cells are treated with a Hh antagonist, a cell death effect is not expected. This expectation is confirmed by the consistent results obtained in the work pertaining to lung cancer cells (see column 35, lines 46-59) and hepatoma cells (see column 68, lines 13-23). Such cells were actually treated with a specific inhibitor of hedgehog signaling. Treatment of cancer cells with a hedgehog antagonist was found to cause inhibition of proliferation of said cells, and pertaining to the lung cancer cell treatments, *Beachy et al '970* states specifically that said findings in “*transformed lung tissue ... therefore indicates that the subject method can be used as part of a treatment of lung carcinoma and adenocarcinomas, and other proliferative disorders involving the lung epithelia*” (column 35, lines 46-59, emphasis added). The skilled artisan further takes notice that the proliferation inhibited cancer cells treated with a hedgehog antagonist were examined by microscopy (which ordinarily allows detection of apoptosis if it occurs) and that no evidence of an induction of apoptosis effect is seen or mentioned (see the *Fujita E et al*

1997 publication cited in *Beachy et al '970*, column 36, lines 46-47). Similarly, no induction of apoptosis is described for the hepatoma cells treated with a Hh antagonist. The skilled artisan also recognizes that whereas the generalized teaching that is made (column 40, line 57 to column 41, line 5) is based on the well-known prior art knowledge that the conventional cancer chemotherapeutics and radiation therapy typically requires cell proliferation for causation of the programmed death (apoptosis) of cancer cells, the statement on column 33, lines 24-26 is without a supporting evidence therein or elsewhere (e.g. in a cited prior art document). Thus, the mention of a possible apoptotic effect in column 33, lines 24-26 is self-contradicted by the actual experimental treatments described in *Beachy et al '970* and as such would be relegated by the skilled person in the art to the realm of the fantastical, rather than enabled disclosure. Since *Beachy et al '970* states, immediately following col. 33, lines 24-25 that the subject method may therefore be used to treat well known epithelial cancers (e.g. ependymomas, see col. 33, lines 26-29), the skilled person, taking note of the actual experimental inhibition of proliferation effect on epithelial cells and not a cell killing effect (col. 40, lines 57-58) would consider the statement in col. 33, lines 26-29 to accord further with an inhibition or cessation of proliferation effect, rather than with cell killing.

iii) Before finally relegating the unsupported, self-contradictory statement at column 33, lines 24-26, speaking about possibility of apoptosis, to the realm of fantasy, the skilled artisan might be motivated to see if *Beachy et al '970* describes actual experiments treating transformed cells with a Hh antagonist elsewhere to achieve apoptotic cells. A search through *Beachy et al '970*, however, does not provide any such experimental result. Rather it confirms the ineffectiveness of this statement as an enabling teaching.

Elsewhere in the prior art the skilled artisan finds that International patent application WO 99/52534, published in October 1999, claims priority to both the *Beachy et al* '970 application (US 09/090622) and the *Beachy et al* '970 priority application (US provisional 60/081186), and has largely overlapping disclosures (identical word-by-word over extended passages). WO 99/52534 describes on page 102, lines 23-30 experiments where transformed cells were treated with a specific inhibitor of hedgehog signaling and it is stated therein that "reduction of β -galactosidase activity appears from the specific inhibition of Shh signaling, rather than from cell toxicity." Thus, the skilled person learns from the WO 99/52534, a *Beachy et al* '970 related application, that the treatment of transformed cells with a Hh antagonist did not cause cell toxicity. A search for other publications of the *Beachy et al* '970 inventors also produces WO 01/27135, which reports that transformed cells were treated with a specific inhibitor of hedgehog signaling and states that "*Significant toxicity (microscopically visible cell death ...) was not observed, even at the highest doses of compounds used*" (see WO 01/27135, page 13, lines 31-32, emphasis added). Thus, the skilled person finds out that even after filing *Beachy et al* '970, the named inventors had not found conditions under which they had observed cell death caused in the treatment of transformed cells according to a "subject method."

In this context, the skilled person has no more basis to believe that the transformed cells described in column 33, lines 24-26 can be induced to become apoptotic, than he/she has to believe that the "subject method" will be effective in treating each and every other members of the fantastical list provided in Appendix A. Taking the teachings of *Beachy et al* '970 as a whole, the skilled artisan would conclude that a Hh antagonist can be used to inhibit proliferation

of transformed cells and that in accord with the explicit generalized teaching of *Beachy et al '970* (column 40, lines 57-58), the transformed cells treated with a Hh antagonist will not be likely to show any evidence of cell death, apoptotic or otherwise. Thus, *Beachy et al '970* column 33, lines 24-26 cannot be declared anticipating presently claimed invention.

4. Column 41, lines 17-24

The statements quoted in the Office Communication from column 41, lines 17-24 of *Beachy et al '970* similarly are made without exemplification or other support and directly contradict other teachings in *Beachy et al '970* as already pointed out. A skilled artisan would take into account the whole of a document and would look for support for a disclosure in the document itself and/or in the rest of art. The actual experimental findings described in *Beachy et al '970* with a Hh antagonist and in the rest of prior art is the causation of an inhibition of differentiation effect on cells, in accord with the wisdom in prior art that Hh proteins act to induce differentiation of various cell types (see the 6/11/2007 Amendment). Numerous publications describing actual treatment of transformed cells, including epithelial tumor cells, with a specific inhibitor of Hh/Smo signaling were also present in prior art but there was no instance of a demonstration of induction of differentiation and/or apoptosis of said cells (see *e.g.* the publication cited on column 35, lines 46-47 in *Beachy et al '970*; see the 1/10/2007 and 6/11/2007 Amendment for further examples).

At least for the particularized reasons discussed above, the aforementioned quotations from *Beachy et al '970*, absent exemplification or other support, cannot be considered anticipating. Otherwise every possible “effect” of a subject method treatment, even explicitly contradictory effects would be routinely listed in patent disclosures and contended to be

anticipating as to whichever was obtained. Preventing reliance on such useless disclosures is a reason why the “undue experimentation” prohibition exists in patent law.

D. *Beachy et al '970* - Treatment of Carcinomas does not Meet Every Recitation of any Pending Claim

Finally, a view is taken in the Office Communication that *Beachy et al '970* contemplates treatment of carcinomas, particularly the basal cell carcinomas, by use of a pharmaceutical composition comprising a subject Hh antagonist and therefore the present claims are anticipated. Said contemplations and disclosures quoted in the Office Communication do not anticipate the presently claimed invention. “Treatment” of a particular disorder in medical practice can entail production of very different technical effects and therapeutic outcomes. The rejected claims (2-6, 8-9, 11-12, 29-30 and 33-40) require production of a specific effect, apoptosis (2-6, 8-9, 11-12, 29-30 and 33-39) or differentiation (claim 40) that was not found in any of the prior art treatments.

All that can be derived unambiguously from the whole of *Beachy et al '970* (which encompasses ambiguous, self-contradicting and inoperative teachings) is that administration of a compound said to be a Hedgehog antagonist can be used to achieve inhibition of proliferation and inhibition of differentiation effects in certain cells in association with the inhibition of Hedgehog signaling (see the 6/11/2007 Amendment). The *Beachy et al '970* claims also speak of administering a compound said to be a Hedgehog antagonist to a patient having “a hyperproliferative disorder” which includes carcinomas (see claims 1, 3-6, 14-16). It is only clear that what is contemplated in terms of treatment of carcinomas, particularly basal cell carcinoma, is the causation of an inhibition of proliferation effect in the carcinoma cells (“...pharmaceutical preparations of the invention are intended for the treatment of hyperplastic ...

as well as... neoplastic epidermal conditions such as those characterized by a high proliferation rate for various skin cancers, as for example basal cell carcinoma"; column 41, lines 25-31). It is well established that the causation of an inhibition of proliferation effect on cancer cells does not anticipate induction of differentiation and/or apoptosis of them (see the 6/24/2005, 3/9/2006 and 1/10/2007 Amendments).

It is also to be emphasized (with respect to claims 2-6, 8-9, 11-12, 29-30 and 33-39) that in the presently described treatment the decrease of size and disappearance of tumors is achieved by a selective and efficient causation of the death and removal of tumor cells by apoptosis, which is a specific form of cell death distinct from others (see *e.g. Willingham MC, The Journal of Histochemistry and Cytochemistry* 1999; 47: 1101-1109; a copy is filed herewith). Unlike the well known damaging of plasma membrane and cell lysis during the cell death due to various toxic agents and during necrosis, the plasma membrane of apoptosing cells is not damaged to release the cellular contents to tissue environment (*Willingham MC* 1999, *ibid*). Thus, the severe inflammatory reaction that in general accompanies other forms of cell death (*e.g. necrotic cell death*) is not a consequence of the induction of apoptosis (*Willingham MC* 1999). The causation in a tumor-bearing patient of the death and removal of tumor cells by inducing their apoptosis in a selective, non-genotoxic and efficient manner as described in the present application makes the instant treatment both distinguished and advantageous over treatments known in prior art.

The analysis of the prior art presented herein and filed with earlier Amendments in the present application further show that the claimed invention is novel over the entire prior art. It is also clear that the presently claimed invention is not inherently present in prior art. For all of these specific reasons *Beachy et al'970* does not anticipate the presently claimed invention.

II. Claim Rejections - 35 USC. § 103

Claims 2-6, 8-9, 11-12, 29-30 and 33-40 have been rejected as being obvious in view of *Lamb JR et al* (WO 00/74706), *Taipale J et al*, *Nature* 2000; 406: 1005-1009 and *Oro AE et al*, *Science* 1997; 276: 817-821. The rejections are traversed. The cited prior art do not render the presently described and claimed subject matter obvious. Rather, the presently claimed invention was highly unexpected and surprising in view of prior art, including *Lamb JR et al*, *Taipale J et al* 2000 and *Oro AE et al* 1997.

A. *Lamb JR et al*'s Teachings as a Whole

Lamb JR et al discloses an unlimited number of compounds that may inhibit Hh signaling and/or a signaling pathway which is a target of Hh signaling and discloses a long list of highly heterogenous disorders to be treated by the administration of one of said compounds. This list, like that of *Beachy et al '970*, is once again high fantasy on its face (see page 29, line 8 to page 32, line 17).³

Furthermore, the teaching is inoperative in entire categories of the disorders taught to be treatable. For example, trauma or compression of the CNS (page 31, line 27), multiple sclerosis (page 30, line 1) and the related demyelinating nervous system diseases (*e.g.* myelitis, encephalomyelitis; see page 31, lines 22-23) are known to be worsened following administration of a specific inhibitor of Hh signaling (see *e.g.* the paragraph bridging page 8 and 9 in the 6/11/2007 Amendment and the paragraph bridging page 10 and 11 in the 3/9/2006 RCE With Amendment; see also *Akazawa C et al* 2004 and *Mastronardi FG et al* 2004 publications filed

³ Excerpts from *Lamb JR et al* are included in Appendix B, Attached.

therewith). Once again, a skilled person must carry out an undue amount of experimentation to determine which teachings in *Lamb JR et al* are operative and which ones are not.

Cancer is included among the disorders that are enlisted as being treatable, but there is no description of a cancer treatment in *Lamb JR et al*. The actual experimental findings are described on page 40, line 23 to page 48, line 10 and in the associated figures. It is described therein that overexpression of Shh in the lung tissue of mice causes lung epithelial cell proliferation and leads to epithelial hyperplasia (page 42, line 7 to page 43, line 16). Human patients with fibrosing alveolitis and the mice having lung tissue damage are described to show upregulation of Hh signaling in the lung tissue. Finally, overexpression of the Hedgehog-Interacting-Protein (HIP, a natural antagonist of Hh signaling) in murine lung is described to provide a reduction of the epithelial hyperplasia of lung tissue following damage as assessed by Ki-67 staining (page 45, line 24 to page 46, line 22). Evidence of inhibition of Hh signaling in the lung tissue overexpressing HIP is also presented.

Thus, the causation of an inhibition of proliferation effect in association with the inhibition of Hh signaling is what a skilled person can derive from *Lamb JR et al* as an expected effect of administering a Hh antagonist. Causation of an inhibition of proliferation effect on epithelial cells is also what is contemplated in *Lamb JR et al* at following administration of a Hh antagonist (“Slides from...treatment groups were stained for a proliferation index marker; Ki-67, to provide evidence that the lung epithelia of SPC-shh mice were actively proliferating”; page 43, lines 10-16). Similarly, *Lamb JR et al* claims treatment of epithelial cell hyperplasia by administering a therapeutically effective amount of an inhibitor of Hh signaling (see claim 12).

It is well known in art that ‘treatment’ of a particular disorder in medical practice can cause very different technical effects and therapeutic results. *Lamb JR et al* has no description of

a cancer-bearing subject and all a skilled artisan can derive from *Lamb JR et al* as a motivation to administer a Hh antagonist to a cancer patient is to achieve, hopefully, an inhibition of proliferation of the cancer cells. The skilled person had been aware of the causation of an inhibition of proliferation of the cancer cells originating from lung epithelium following administration of a specific inhibitor of Hh signaling (see the *Fujita E et al* 1997 filed with the 3/9/2006 RCE with Amendment).

Lamb JR et al teaches that whereas a therapeutically effective daily dose of the compounds of invention is likely to be in an exemplary range given therein, the actual dosage to be administered will be determined according to the response of the particular patient (page 38, lines 4-19). The response in a cancer patient that a skilled person can expect to obtain in view of *Lamb JR et al* is an inhibition of proliferation of the cancer cells. Thus, a skilled person motivated by *Lamb JR et al* to administer a Hh antagonist to a cancer patient will administer a dose to obtain an inhibition of cancer cell proliferation in the patient. Being familiar with the serious problems of prior art non-surgical cancer treatments arising from the damaging of normal stem cells, the skilled person would be particularly discouraged to exceed a minimal dose producing an inhibition of proliferation of the cancer cells, taking note that normal stem cells have been described to be absolutely dependent on Hh signaling (see *Zhang Y et al* 2001 filed with the 1/10/2007 Amendment).

Nothing in *Lamb JR et al* or in the rest of prior art leads a skilled person to expect that a specific inhibitor of Hh/Smo signaling could be used to obtain the presently claimed effects. Rather, the wisdom and experimental findings in prior art were actually leading the skilled person away (see item I above). On the other hand, contrary to the situation in of the prior art, numerous post-published investigations have independently confirmed that a specific inhibitor of

Hh signaling can indeed be used to obtain the technical effects and therapeutic outcome described in this application but a dose far exceeding a minimal dose producing inhibition of proliferation of the tumor cells is required (see the 1/10/2007 and 6/11/2007 Amendments). Compounds and products having identical or similar composition to those described in prior art are used in the presently claimed method to obtain technical effects that are highly unexpected and surprising in view of entire prior art. It is also clear that said effects are not an innate property of the previously known compounds and products.

The quotation in the Office Communication from *Lamb JR et al* stating that the disease states resulting from loss of normal function of the regulators of Hh signaling are contemplated to be treated by administering Hh antagonistst does not obviate the presently claimed invention at least because different (opposite) effects can be produced on Hh signaling depending on the particular regulator.

Further objective evidence that the presently claimed invention was highly unexpected and surprising not only in view of *Lamb JR et al* but the entirety of prior art is given below.

B. Taipale J et al's Teachings as a Whole

Taipale J et al 2000 describes that cyclopamine or a derivative thereof (KAAD-cyclopamine) can be administered to transformed cells showing excessive activity of Hh/Smo signaling to obtain blocking of Hh signaling and to produce inhibition of proliferation of said cells. The proliferation-inhibited cells were examined by microscopy (see *e.g.* Figure 3) ***but no description of or evidence of an induction of differentiation and/or apoptosis of said cells is described or seen.*** The "mechanism-based" treatment of tumors mentioned in the Office Communication that a skilled artisan can derive from *Taipale J et al* 2000 is therefore causation

of an inhibition of proliferation of the tumor cells in association with the inhibition of Hh/Smo signaling. Nothing in *Taipale J et al* 2000 or in the rest of prior art leads a skilled person to expect that cyclopamine or KAAD-cyclopamine could be used to produce the presently claimed effects in a tumor-bearing patient. Reversal of the activation of Hh/Smo signaling in transformed cells where it becomes undetectable (see Figure 3 in *Taipale J et al* 2000) or inhibition of proliferation of said cells cannot produce the presently described and claimed effects on tumor cells in a tumor-bearing patient (see the 3/9/2006 RCE With Amendment, 1/10/2007 Amendment and 6/11/2007 Amendment).

At least for the aforementioned reasons *Taipale J et al* 2000 cannot make presently claimed invention obvious and a skilled person motivated or induced by *Taipale et al* 2000 to block Hh signaling to treat tumors would not be able to obtain the presently described therapy results.

C. Oro AE et al's Teachings as a Whole

Oro AE et al 1997 points out to the upregulation of Hh signaling as a consequence of the inactivating patched mutations and to the causation of Basal Cell Nevus Syndrome (BCNS) by the haploinsufficiency of same gene. Considering the markedly increased formation of BCC's and other tumors in the BCNS patients, identification of the inactivating patched mutations in sporadic tumors as well and the similar effects of these mutations and of excessive Hh on Hh signaling, *Oro AE et al* 1997 evaluates overexpression of Hh on the occurrence of tumors. It is described that the transgenic mice generated to have Shh overexpression in skin developed multiple epidermal *proliferations* indistinguishable from the human BCC's in terms of morphological features and in terms of expressed genes.

Nothing in *Oro AE et al 1997* leads a person skilled in the art to expect that the administration of cyclopamine or of another specific inhibitor of Hh signaling to BCC's or to the other tumors showing Hh signaling overactivity, in a sufficiently high dose, can produce an ***induction of differentiation and/or apoptosis of tumor cells***. *Oro AE et al 1997* arguably might have given inspiration to a skilled person to administer a specific inhibitor of Hh signaling to a patient having such a tumor to inhibit ***proliferation*** of the tumor cells. However, an administration aiming for inhibition of proliferation of the tumor cells does not provide the presently described and claimed effects on tumor cells as already explained.

D. Further Objective Evidence of Unobviousness

The Applicant agrees that there was a recognized need in art to solve the well-known problems associated with the existing tumor treatments. It is also true that a person of ordinary skill in art was aware of the widespread occurrence of upregulated Hh/Smo signaling in tumors (both in NBCS-associated tumors and in sporadic tumors, as pointed out also in the prior art cited in the Office Communication (*Oro AE et al 1997*; *Beachy et al '970*, see e.g. column 35, lines 46-59; column 42, lines 43-49; *Taipale J et al 2000*)). It is further true that the skilled person would have been motivated by this need and knowledge in prior art to attempt an administration of a specific inhibitor of Hh/Smo signaling to a tumor bearing patient. The skilled person having said motivation would be guided by the information available in prior art about Hh/Smo signaling and about the expected effects of a specific inhibitor of it in a tumor-bearing patient besides his/her general knowledge about tumor treatment.

Numerous compounds that inhibit Hh/Smo signaling specifically were well-known and available in prior art (see the 9/6/2007 Amendment). Several of such compounds had been

administered onto various transformed cells, including human lung cancer cells and cells having constitutively activated Hh/Smo signaling. In accord with the earlier reports of promotion of proliferation of various cell types by Hh/Smo signaling, an inhibition of proliferation effect was commonly described on the transformed cells treated with such compounds (see item I above). The skilled artisan motivated by the prior art would thus aim to obtain an inhibition of proliferation effect on the tumor cells in the tumor-bearing patient.

Neither the induction of differentiation effect nor the induction of apoptosis effect described in the present application would be an expected effect for the skilled artisan. Rather, both the experimental findings and wisdom in the prior art were leading him/her away from considering any of said effects as set forth below.

Hh proteins were discovered originally as determinants of patterning in the developing embryo where they were found to act to induce differentiation of various cell types. Normally expected effect of a Hh antagonist on target cells in terms of their differentiation would thus be an inhibitory effect. This expectation was borne out in numerous prior art investigations and indeed the documentation of cyclopamine's and jervine's inhibition of Hh/Smo signaling specifically was based on the demonstration that they selectively inhibited the differentiation events induced by a Hh protein (Shh) (see *Cooper MK et al 1998* and *Incardona JP et al 1998* filed with the 9/6/2007 Amendment). Furthermore, none of the numerous prior art publications describing treatment of transformed cells with a specific inhibitor of Hh/Smo signaling had a demonstration of an induction of differentiation.

None of the numerous prior art publications describing treatment of transformed cells with a specific inhibitor of Hh/Smo signaling had shown an induction of apoptosis effect, either. Furthermore, prior art investigations where cyclopamine (a specific inhibitor of Hh/Smo

signaling) was administered onto both normal cells and well known tumorigenic cells had concluded that the latter cells, unlike the normal cells, are “resistant to cyclopamine-induced cell death” (*Dunn MK et al, Developmental Dynamics* 1995; 202:255-270). Accordingly, ***not only was the presently described and claimed induction of apoptosis of tumor cells by use of cyclopamine unexpected from the prior art, the attainment of this result in vivo with the described selectivity and efficiency sparing the normal cells was also highly unexpected.***

Hh/Smo signaling had been detected in prior art in various normal cells in adult organisms. Besides this information, the skilled person was acutely aware of the serious problems of the damaging of normal stem cells by the prior art non-surgical treatments for cancer and he/she was further aware that normal stem cells are absolutely dependent on Hh/Smo signaling (*Zhang Y et al* 2001, *ibid*). The skilled artisan motivated by prior art to administer a specific inhibitor of Hh/Smo signaling to a tumor-bearing patient had therefore multiple reasons for proceeding cautiously and not to administer a dose exceeding a minimal dose that will be effective in inhibiting proliferation of the tumor cells. He/she is experienced with adjusting doses of prior art medicaments according the expected effects. He/she would start administering in minimal amounts and gradually increase the dosage until the inhibition of proliferation of tumor cells taught in prior art is achieved without a need for telling to him/her to do so.

The skilled artisan motivated by prior art to administer a specific inhibitor of Hh/Smo signaling to a tumor-bearing patient had also a fundamental reason to aim for an inhibition of proliferation effect on the tumor cells. A direct role of Hh/Smo signaling was described in prior art in stimulation of cell proliferation of cells stemming from the well-established inhibitory effect of normal patched on Hh/Smo signaling (*Barnes EA et al, The EMBO Journal* 2001, 20:2214-2223; a copy is filed herewith). *Barnes EA et al 2001* refers to the oncogenicity of

inactivating patched mutations and points out that the identified direct inhibition of cellular proliferation by normal patched brings an explanation to the oncogenic effects of said patched mutations which cause constitutive activation of Hh/Smo signaling.

Inhibition of proliferation of tumor cells anticipates neither differentiation nor apoptosis of said cells. As has been well established in the record of this case, a minimal dose of a specific inhibitor of Hh/Smo signaling effective to inhibit proliferation of tumor cells is clearly *ineffective* to provide the presently claimed effects on said cells (see the 3/9/2006 RCE with Amendment and the 1/10/2007 Amendment). Thus, a skilled person motivated by and following the teachings in prior art to administer a specific inhibitor of Hh/Smo signaling to a tumor-bearing patient did not inherently reach to the presently claimed effects on tumor cells. This failure in fact was a common feature of several prior art treatments of tumor cells, as discussed above. The evidence of record thus conclusively establishes that the skilled person was not led to obtain a decrease of size or disappearance of the tumor of patient by the teachings of the cited documents.

Finally, the presently described induction of apoptosis of tumor cells *in vivo* with

- (i) the selectivity sparing normal cells (including the undifferentiated cells in epidermis basal layer and in hair follicles well known to contain cells having stem cell features), and
- (ii) the efficiency providing the described rapid decrease of size and disappearance of tumors

was highly unexpected in prior art not only in view of the previously described comparative effects on normal and tumorigenic cells (*Dunn MK et al* 1995, *ibid*) but also in view of the vast clinical experience and wisdom in prior art that viewed the above-mentioned effects (i) and (ii)

as *unattainable on theoretical grounds* (see e.g. the review article “*Apoptosis and the Dilemma Of Cancer Chemotherapy*”, Hannun YA, *Blood* 1997;89:1845-1853; a copy was filed with the 1/10/2007 Amendment).

E. The Examiner's Conclusion Of Obviousness Is Unsupported

The Examiner makes on page 17 of the Official Communication three findings of fact:

- (i) at the time of the invention, there was a recognized need in the art to solve the problem of developing antitumor agents that are specific to certain signaling pathways such as Hedgehog/*Smoothened*;
- (ii) there were a finite number of predictable solutions for treating tumors wherein Hedgehog/*Smoothened* is implicated (e.g., treating such tumors with an inhibitor of Hedgehog signaling); and
- (iii) one of ordinary skill in the art could have pursued the known options with a reasonable expectation of success (e.g., administering cyclopamine, which inhibits the Hedgehog response, to tumors such as basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and other human tumors that are associated with mutations that activate the proto-oncogene *Smoothened* or that inactivate the tumor suppressor *Patched*).

From these findings, the Examiner reaches to a conclusion that the instant claims would have been obvious stating that

“a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense”.

The Applicant traverses the conclusion as incorrect and not in accordance with the facts in this case. It is also submitted that in formulating said opinion of obviousness, substantial evidence of record has been ignored, the documents and prior art have been improperly considered in hindsight and viewed in light of the present disclosure rather than from the perspective of prior art.

With regard to the third finding of Examiner (*iii* above), it must be pointed out that the “reasonable expectation of success” to a person of ordinary skill in art was the causation of an inhibition of proliferation effect on the tumor cells so as to obtain inhibition of further growth of tumor. Not even from the incomplete findings *i* to *iii* mentioned on page 17 of Office Communication is it possible to reach to the conclusion that “the instant claims would have been obvious”. This is at least because the instant claims speak of induction of apoptosis of the tumor cells to obtain decrease of size / disappearance of tumor besides induction of differentiation of tumor cells and all of these are clearly distinguished from the causation of an inhibition of tumor cell proliferation to obtain inhibition of tumor growth.

The evidence of record, taken as a whole, supports the following findings of fact:

- (i) At the time of the invention, there was a recognized need in art to solve the problem of cancer treatment, the existing treatment modalities being poorly effective even when one accepts the common early adverse effects like the falling of hair and the late effects that disturbingly include the causation of secondary cancers unrelated to the primary.
- (ii) In tumors exhibiting upregulated Hh/Smo signaling for one reason or another, administration of an inhibitor of Hh/Smo signaling onto the tumor cells would have been considered as a potential approach to tumor treatment.
- (iii) Upregulation of Hh/Smo signaling was described in numerous tumors belonging to various histopathological classes as a result of genetic/epigenetic changes causing
 - loss-of-function of Patched and/or
 - gain-of-function of Smoothened and/or
 - gain-of-function of Gli1/Gli2 and/or
 - overexpression of a Hh protein.

How this widespread upregulation of Hh/Smo signaling in the various tumors wherein it was described might be contributing to the occurrence of said tumors was also investigated. It was found that Hh/Smo signaling has a direct stimulatory effect on cellular proliferation emanating from a direct effect of Patched on cellular proliferation. In accord, several investigations were published describing that application of a specific inhibitor of Hh/Smo signaling onto various tumor cells exhibiting upregulated Hh/Smo signaling produced an inhibition of proliferation effect. A person of ordinary skill in art would have therefore

contemplated to administer a Hh antagonist to a tumor-bearing patient with a reasonable expectation of success in inhibition of tumor cell proliferation.

- (iv) Hh/Smo signaling was well known to have detectable activity in various normal cells in an adult. These included neurons and in particular various normal cells with stem cell features. A person of ordinary skill in art contemplating to administer a Hh antagonist to a tumor-bearing patient would thus be hesitant and highly cautious fearing the adverse effects on normal cells.
- (v) Normal stem cells in an adult were found to have an absolute dependence on Hh/Smo signaling and not to be able to proliferate in its absence.
- (vi) A common and well known adverse effect of prior art chemotherapy/radiotherapy protocols for cancer treatment was the causation of damage to the normal stem cells. An ordinary skilled artisan was acutely aware of the severe limitations of the applicability and clinical utility of prior art treatments because of said damaging. He/she would therefore be further hesitant and warned about administering a Hh antagonist and he/she would certainly aim not to exceed a dose that will be effective in producing the expected effect of an inhibition of tumor cell proliferation.
- (vii) Adjustment of the dosage of a medicament according to the expected effects in the treated patient was common knowledge in prior art. Starting at a dose below that of a dose expected to produce a known effect, gradually increasing until the expected effect is observed and stopping administration at the minimum dosage effective in producing the expected effect was something the skilled artisan was already well versed. Similar instructions were given in a number of prior art documents describing an inhibition of proliferation effect by use of a Hh antagonist.
- (viii) Inhibition of tumor cell proliferation and inhibition of tumor growth could be readily determined in prior art by routinely used laboratory methods and imaging modalities.
- (ix) Prior to the applicant's invention, several treatments of tumor cells with a specific inhibitor of Hh/Smo signaling were undertaken *in vitro* and *in vivo*. The only results reported in the publications describing such treatments were consistent with an anti-proliferative effect.
- (x) Hh family of proteins were discovered originally for their effects on the patterning of developing embryo where they acted to induce differentiation of various cell types. A specific inhibitor of Hh/Smo signaling would thus normally be expected to have an inhibitory effect on differentiation. Indeed a selective inhibition of the differentiation events induced by a Hh protein was a commonly employed criterion in prior art in identifying compounds that inhibit said signaling specifically.

- (xi) Although various tumor cells were treated with a specific inhibitor of Hh signaling in prior art, an actual demonstration of induction of differentiation of the treated tumor cells was lacking.
- (xii) Prior to applicant's invention, no one had ever described having accomplished induction of apoptosis of any tumor cell by treatment with a specific inhibitor of Hh/Smo signaling although several such treatments *in vitro* and *in vivo* were described and the treated cells were examined by microscopy which ordinarily enables detection of apoptosis
- (xiii) In most conventional drug treatments of cancer, induction of apoptosis of cancer cells was well known to be dependent on or facilitated by the proliferation of cancer cells. For that reason, prior or simultaneous administration of the stimulators of proliferation with conventional cancer chemotherapeutics was widely used. *Beachy et al '970* and *Dudek et al* had also referred to this fact and stated that because a subject Hh antagonist will in general exert an inhibition of proliferation effect, such a compound could be used to obtain an inhibition of apoptosis effect. This, they taught, could be useful against the well known hair loss in cancer patients undergoing chemo- or radiation-therapies.
- (xiv) Prior art investigations comparing effects of the treatment with a specific inhibitor of Hh/Smo signaling on normal and tumor cells had concluded that unlike normal cells, the transformed cells are resistant to the cell killing effect of such a treatment. Thus, not only the use of a specific inhibitor of Hh/Smo signaling for inducing apoptosis of tumor cells was unexpected but the attainment of said effect *in vivo* with unprecedented efficiency and selectivity sparing the adjacent normal cells was also *highly unexpected and surprising*.
- (xv) Persons of ordinary skill in the art could have, and actually did, pursue using specific inhibitors of Hh/Smo signaling for treatment with a reasonable success as expected in prior art, observing an inhibition of tumor cell proliferation but these investigators never reported an induction of tumor cell apoptosis.
- (xvi) The application teaches, and numerous post-published investigations have independently confirmed that a dosage of a specific inhibitor of Hh/Smo signaling necessary for induction of apoptosis of tumor cells is magnitudes greater than the minimum dosage effective in producing an antiproliferative effect.
- (xvii) Prior to the applicant's invention, no one had ever described having accomplished decrease of size or disappearance of a tumor in a tumor-bearing subject by use of a specific inhibitor of Hh/Smo signaling. The shrinking / disappearance of a tumor in a patient requires an *efficient* and *selective* elimination of the tumor cells from his/her body. A mere antiproliferative effect on tumor cells cannot provide decrease of size or disappearance of a once existing tumor. Causation of decrease of size / disappearance of a tumor differs clearly in its capacity to restore health

from causation of an anti-proliferative effect on tumor cells which produces inhibition of tumor growth.

- (xviii) Prior to applicant's invention, causation of the death and removal of tumor cells in a patient with the efficiency causing disappearance of tumor and with the selectivity sparing normal cells was considered *an unattainable goal on theoretical grounds* as well as in view of the vast clinical experience. The generally held wisdom in art was against the achievability of presently described therapeutic results.
- (xix) Tumor cells can be killed also by non-apoptotic means and numerous treatments with various cytotoxic compounds (including steroidal compounds) were described in prior art that caused a non-apoptotic death of the tumor cells. Compared to the typically severe inflammatory reaction that follows non-apoptotic modes of tumor cell death, the tumor cell removal by apoptosis is safer and has substantial health benefits.
- (xx) Unlike conventional chemotherapy / radiotherapy protocols for tumor treatment relying on the causation of damage to the genetic material for induction of tumor cell apoptosis, the presently described treatment induces tumor cell apoptosis in a non-genotoxic manner. Induction of tumor cell apoptosis without causation of damage to the genetic material brings highly desired safety benefits in tumor treatment that were previously unavailable.
- (xxi) The present method of tumor treatment providing the apoptotic death and removal of tumor cells without reliance on genotoxicity brings a previously unknown life-saving opportunity to those patients having an inoperable tumor that is resistant to conventional chemotherapy / radiotherapy because of mismatch repair deficiency of DNA or loss of normal p53 functions in tumor cells. Because these functional deficiencies are by themselves tumorigenic, a large number of tumor patients are known to exist belonging to this distinct subpopulation. In these patients, the conventional treatments that induce tumor cell apoptosis through causation of extensive genotoxicity cannot provide removal of the tumor cells and a mere inhibition of tumor cell proliferation cannot correct the consequences of an already existing tumor cell load (e.g. paraneoplastic syndromes). The presently described invention brings therefore a previously unknown advantageous solution to the problem of the treatment of this large subpopulation of tumor patients.

At least for the aforementioned reasons the presently claimed subject matter satisfy the requirements of 35 U.S.C. §103 for patentability.

F. Obviousness Rejection Over *Beachy et al '970*

Claims 7 and 10 have been rejected as obvious from *Beachy '970* as applied to claims 2-6, 8-9, 11-12, 29-30, and 33-40. The rejection fails for at least the reasons given that *Beachy '970* does not anticipate claims 2-6, 8-9, 11-12, 29-30, and 33-40.

III. Claim Rejections - 35 U.S.C. § 112 - 1st Paragraph

Claims 2-12, 29-30, 33-35 and 37-40 have been rejected stating that said claims contain subject matter not described in the specification in such a way to reasonably convey to a skilled person that the inventors, at the time the application was filed, had possession of the claimed invention. The applicant does not agree.

A. No New Matter Has been Introduced

Opinion is expressed in the Office Communication that no specific support exists in the specification as originally filed for the language in claims 33, 37, 39 and 40. Contrary to said opinion, specific support exists in the originally filed specification as shown below.

(i) The language “a compound that binds specifically to a receptor to which cyclopamine binds” in claim 33.

The originally filed specification depicts the cyclopamine molecule and indicates that it is a *Veratrum* alkaloid known to inhibit Hedgehog/Smoothed (Hh/Smo) signaling and the prior art scientific publications cited in that respect describe a selective inhibition by cyclopamine of the differentiation events induced by a Hh protein to conclude that cyclopamine specifically inhibits Hh/Smo signaling (see page 2, line 20 to page 3, line 6). The second paragraph on page 10 of specification indicates that molecules can be derived from cyclopamine or synthesized in

such a way that they “exert similar receptor binding properties and biological effects as cyclopamine” (lines 8-10) and “bind specifically to the same biological target to exert the biological effects of cyclopamine” (lines 15-16). Thus, specific support exists in the originally filed application for the rejected claim language in claim 33.

(ii) The language “a compound that exerts similarly specific inhibition of Hedgehog/Smoothed signaling as cyclopamine” in claim 37.

The originally filed application has specific support for the rejected claim language in claim 37 at least for the reasons given above in relation to claim 33.

(iii) The language “another compound that specifically inhibits Hedgehog/Smoothed signaling” in claims 39, 40.

Cyclopamine was well known in prior art to be a specific inhibitor of Hh/Smo signaling and the originally filed specification refers to this fact (item *i* above). The skilled person knows that a molecule can be derived from cyclopamine or synthesized in such a way to exert said well known biological effect of cyclopamine as mentioned in the specification (page 10, lines 8-10, 22-26). Thus, the originally filed application has specific support for the rejected claim language in claims 39, 40.

B. There is Adequate Description of the Claimed Subject Matter

In determining compliance with the written description requirement “the fundamental factual inquiry is whether the specification conveys with reasonable clarity *to those skilled in the art* that, as of the filing date sought, applicant was in possession of the invention as now claimed” (emphasis added) See MPEP 2163. “A patent need not teach, and preferably omits, what is well known in *art*”; “Information which is well known in the art need not be described in detail in the specification”, *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir

1991); *Hybritech, Inc v. Monoclonal Antibodies, Inc.*, 802 F .2d 1367, 1379-80, 231 USPQ 81,90 (Fed. Cir 1986), cert denied, 480 U.S. 947 (1987); see MPEP 2163. “There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper”, *In re Swineheart*, 439 F .2d 210, 169 USPQ 226(CCPA 1971).

The factual determination of the compliance with written description requirement thus requires

- (i) determining the teachings in the originally filed application and
- (ii) determining the state of the art at the time of the filing of application

The written description analysis presented below starts by pointing out to what was well known in prior art and reference is made to the teachings in the originally filed application as appropriate.

1. Prior Art Concerning Hedgehog/Smoothed Signaling, it's Inhibition and it's Upregulation in Tumor Cells

Hh proteins were discovered originally for their effects on the patterning of developing embryo where they acted to induce differentiation of various cell types. Sonic hedgehog (Shh), a member of the Hh family of proteins, was found to be essential for the induction of differentiation of several cell types in developing brain. A loss-of function mutation of Shh was shown to lead to failure of formation of the ventral forebrain (which depended on Shh for development) and thereby to the fusion of eyes (cyclopia) in zebrafish (*Krauss S et al, Cell* 1993;75: 1431-1444; a copy is filed herewith). Cyclopia and other developmental abnormalities characteristic of human holoprosencephaly had long been known to occur because of exposure of developing embryo to cyclopamine and other teratogenic *Veratrum* alkaloids (see *e.g. Keeler RF*

1970 filed with the 1/10/2007 dated Amendment). Similarly, the loss-of-function mutations of the gene for Shh were found to cause cyclopia and other features of holoprosencephaly in human and mouse (*Roessler E et al Nature Genetics* 1996;14:357-360; *Chiang C et al Nature* 1996;383:407-413; a copy of each is filed herewith). In accord with these earlier findings, the scientific publications cited on page 3, lines 5-6 of the specification in present application described in 1998 that cyclopamine as well as jervine (another teratogenic *Veratrum* alkaloid) inhibits Hh/Smo signaling specifically (*Cooper MK et al* 1998 and *Incardona JP et al* 1998; filed with the 9/6/2007 dated amendment). That cyclopamine and jervine inhibited the Hh/Smo signaling specifically was deduced from the fact that they selectively inhibited the differentiation events induced by Shh (*Cooper MK et al* 1998; *Incardona JP et al* 1998). Indeed, the same Shh-induced differentiation events inhibited by cyclopamine and jervine were shown earlier to be selectively inhibited by affinity purified antibodies binding and blocking Shh (*Ericson J et al* 1996; filed with the 9/6/2007 Amendment). In prior art, numerous other naturally occurring and synthetic non-cyclopamine molecules with and without a cyclopamine core were also known to inhibit Hh/Smo signaling specifically as demonstrated by selective inhibition of the Hh-induced differentiation events and/or by their effects on Gli proteins (intranuclear executors of Hh signaling) (see the 9/6/2007 Amendment).

General features of Hh/Smo signaling were determined initially in *Drosophila* and were later found to be conserved in diverse organisms, including human. However, as mentioned in the specification of application, a larger number of gene products are found to take part in Hh/Smo signaling in the more advanced organisms. For example, human and mouse were described to have three homologues of the single Hh of *Drosophila* (Shh, Ihh, Dhh) and three homologues of the single Ci of *Drosophila* (Gli1, Gli2, Gli3) which mediate transcription of the

Hh target genes in cell nucleus. The Patched protein was found to act as a receptor of Hh in *Drosophila*. When not liganded by Hh, Patched was shown to act to inhibit the intracellular signal transduction by another transmembrane protein, Smoothened (Smo). Binding of Hh to Patched was determined to relieve the inhibitory effect of Patched on Smo. The relieved Smo was found to initiate a series of events in the cell, resulting in the accumulation of full length Ci protein which directly acted to mediate transcriptional activation of Hh target genes.

As indicated in specification, it was well known in prior art that a loss-of-function of Patched causes upregulation of Hh/Smo signaling. Inactivating mutations of patched were found to cause constitutive upregulation of Hh/Smo signaling in basal cell carcinomas (BCC's) as well as in various other tumors. As the specification points out, Hh/Smo signaling overactivity was well known to occur in tumors also as a result of the genetic changes affecting further downstream elements of Hh/Smo signaling (page 2, lines 11-13; see reviews *Hahn H et al, Journal of Molecular Medicine* 1999;77:459468; *Wicking C et al, Oncogene* 1999;18:7844-7851; see also *Dahmane N et al, Nature* 1997;389:876-881; *Grachtchouk M et al, Nature Genetics* 2000;24:216-217; *Nilsson M et al, Proceedings of the National Academy of Sciences of the USA* 2000;97:3438-3443; copies are filed herewith). Similarly, excessive production of a Hh protein was well recognized to cause Hh/Smo signaling overactivity similar to the loss of Patched function (*e.g. Oro AE et al* 1997 cited in the Office Communication). *Oro AE et al* 1997 described causation of skin tumors indistinguishable from human BCC's in the skin of transgenic mice overexpressing Shh in skin and described further a Shh mutation associated with human tumors in accord with an action of the gene for Shh as an oncogene. *Oro AE et al* 1997 pointed out also to the phenotypic similarities between the Shh overexpressing mice and Basal Cell Nevus Syndrome (BCNS) patients who were well known to develop many tumors because of an

inactivating allele of patched. Besides BCC's, BCNS (also called Nevoid Basal Cell Carcinoma Syndrome, NBCCS) was well known to cause numerous other tumors, including medulloblastoma, fibroma, fibrosarcoma, meningioma, lymphoma, rhabdomyoma, rhabdomyosarcoma and schwannoma (see the 1/10/2007 Amendment).

Thus, it was common knowledge in prior art that Hh/Smo signaling upregulation is widespread in tumors and that it can be caused by genetic/epigenetic changes that affect

- (i) shh to cause gain-of-function and/or
- (ii) patched to cause loss-of-function and/or
- (iii) smoothened to cause gain-of-function and/or
- (iv) gli1/gli2 to cause gain of function.

Further, it was clear that the same histopathologically classified tumor could be caused by gene changes affecting different components of Hh/Smo signaling as shown by the causation of BCC's by changes of type *i*, *ii*, *iii* or *iv* mentioned above (*Oro AE et al 1997; Hahn H et al 1999; Wicking C et al 1999; Dahmane N et al 1997; Grachtchouk M et al 2000; Nilsson M et al 2000*) and by the causation of trichoepitheliomas by changes of type *ii* or *iv* (see *Nilsson M et al 2000*).

2. Written Description Satisfying 35 U.S.C. § 112 – 1st Paragraph

An actual reduction to practice of the claimed invention is a means by which the written description requirement can be satisfied.

The specification in the present application describes actual reduction to practice of the invention on more than 7 tumors belonging histopathologically to the tumor types of BCC or trichoepithelioma or a melanocytic tumor satisfying the functional definition given in claims. The skilled person notices that the Applicant carried out the entire method of treatment on actual

human tumors more than 7 times and each time the described method was applied, the method was successful in producing the claimed effects and decreased size / disappearance of tumor. The skilled person readily understands that the occurrence of the described effects and results cannot be due to chance and could not have been produced if the Applicant was not in possession of the claimed method of treatment.

Numerous post-published investigations independently confirm that the teachings in the presently-claimed invention are operative and adequate to carry out the invention on tumors belonging to numerous different histopathological types (see the 1/10/2007 Amendment for examples). Nothing other than described in the specification and routinely used in prior art is described in these post-published investigations in obtaining presently described technical effects and results. This is further evidence that the skilled artisan, already aware of the widespread occurrence of Hh/Smo signaling overactivity in tumors, could readily carry out the invention once informed about the utilization of Hh/Smo signaling for inhibition of differentiation and apoptosis of tumor cells. Methods for assaying Hh/Smo signaling and markers of differentiation and apoptosis were common knowledge and routinely used in prior art (see *e.g. Willingham MC* 1999 for apoptosis; see the publications filed with the 9/6/2007 dated Amendment for assays of Hh/Smo signaling and differentiation). Thus, identifying “those tumor cells that use the Hedgehog/Smoothed signaling for inhibition of apoptosis or differentiation” was well within the capability of a person of ordinary skill in art once informed about the existence of said tumor cells. Furthermore, if -for the sake of argument- a view like on page 9, paragraph 2 of the Office Communication is taken, it is clear that a functional definition of tumors (or of another species or *genus*) would be generally unacceptable in claims. This is because, before carrying out the invention the skilled artisan must determine that the tumor (or another object of invention) meets

the functional definition. Obviously such a view has not been taken previously by the Office or by courts of law (see e.g. the database of allowed patents at USPTO containing numerous granted patents with claims defining a tumor or another object by functional features; see also *In re Swineheart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)).

In rejecting claims 2-12, 29-30, 33-35 and 37-40, Office Communication states further that inadequate written description exists for the non-cyclopamine compounds that are indicated in the claims to be suitable to use in the described method in place of cyclopamine. Applicant does not agree.

Cyclopamine and other teratogenic *Veratrum* alkaloids were well known in prior art to inhibit Hh/Smo signaling specifically, as documented by their selective inhibition of the differentiation events induced by a Hh protein in chicken embryos. The specification mentions this prior art information (see e.g. page 2, line 20 to page 3, line 6 and the scientific publications cited therein). Furthermore, besides said naturally occurring teratogenic *Veratrum* alkaloids, numerous other compounds were also well known in prior art to be suitable to inhibit Hh/Smo signaling specifically. They included compounds acting on different components of the Hh/Smo signaling and synthetic as well as naturally occurring compounds with and without a cyclopamine core (see the 9/6/2007 dated Amendment). Thus, a skilled artisan would have understood readily that a non-cyclopamine compound that inhibits Hh/Smo signaling specifically could also be used in the presently claimed method of treatment and that the applicant was in possession of such a compound at the time of the filing of application.

The specification mentions that compounds can be synthesized or derived from cyclopamine in such a way that they exert the biological effects of cyclopamine. The skilled artisan could readily determine whether a particular compound is suitable to inhibit Hh/Smo

signaling specifically or not by using the Hh/Smo signaling assays routinely used in prior art. He/she was also aware of *the numerous non-cyclopamine compounds already existing and suitable to inhibit Hh/Smo signaling specifically. The scientific publications cited in the specification also describe examples of such non-cyclopamine compounds* (see the publications cited on page 3, lines 5-6, 13; see *Goodrich LV et al* 1998 cited in the PCT/TRO2/00017 incorporated into this application and filed with the 9/6/2007 Amendment).

The Office Communication quotes from the *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed Cir 1997), *cert denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998); *Enzo Biochem, Inc v Gen-Probe Inc*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) and *Univ. of Rochester v GD Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N Y 2003) in making argument of inadequate written description. The claims at issue in both *Lilly* and *Enzo* cases were directed to DNA sequences. Since it is well known that gene products having different features can be generated from the same DNA sequence (*e.g.* through alternative splicing), the court decisions in said cases affirm the principle that a functional definition of compounds must be clear and must leave no room to uncertainty concerning whether a particular compound would be within or out of the functionally defined category of compounds. It is to be emphasized that that there is not a decision that says that a functional definition of a category of compounds would necessarily be insufficient. In addition, the quotation from the *Rochester* court in rejecting instant functional definition of compounds is misleadingly incomplete. The *Rochester* court makes it clear that there is nothing in principle against a functional definition of compounds. The court points out in its decision that the claim limitation in the *Univ of Rochester* patent was found unsatisfactory because there was no evidence that the Patentee was in possession of even a single compound satisfying the functional definition given in claim. *No compound* was known at the time of the

filing of the application that satisfied said functional definition. In the present case, on the other hand, the skilled person recognizes from the specification and he/she is already aware that numerous compounds satisfying the functional definition given in claims 33, 37, 39 and 40 were known and available for use at the time of the filing of application.

The Office Communication notes that the compounds as instantly claimed must specifically bind to a certain receptor (e.g. claim 33) or specifically inhibit Hh/Smo signaling (e.g. claim 39) (emphasis in the original) and states that this makes the claim language further unacceptable. Applicant does not agree.

Specific binding of a compound to a receptor is a well understood clear definition in art. In case of claim 33, it means that both cyclopamine and said compound inhibit Hh/Smo signaling by binding to the same component of Hh/Smo signal transduction and that the compound, like cyclopamine, does not have a significant effect on another signaling exerted by binding to another receptor molecule. The direct effect of the compound on Hh/Smo signaling can obviously have consequences on other signals in a cell (as mentioned *e.g.* in *Lamb JR et al*, WO 00/74706 cited in the Office Communication) but they are clearly secondary to the primary effect on Hh/Smo signaling. An apt example to illustrate specificity/non-specificity distinction is provided by the Vitamin D3. Binding of Vitamin D3 to the Vitamin D3 receptor protein in the cell nucleus has long been known to have potent effects on calcium metabolism directly originating from said binding. Besides binding to the Vitamin D3 receptor, Vitamin D3 was recently described to be capable of binding also to the Smoothed protein, albeit with a relatively weaker affinity than it is known to have to the Vitamin D3 receptor (see *Bijlsma MF et al*, *PloS Biology* 2006;4:e232; a copy is filed herewith). Thus, Vitamin D3's strong binding to the Vitamin D3 receptor protein to result in significant changes in calcium metabolism precludes

its consideration as a compound that binds specifically to a receptor to which cyclopamine binds to inhibit Hh/Smo signaling. The skilled person would have no difficulty in understanding claim 33. The claim language makes it clear that a compound that alters another signaling directly (*i.e.* not as a consequence of a primary effect on Hh/Smo signaling) is not within the scope of claim 33. Similarly, the claim language “another compound that specifically inhibits Hh/Smo signaling” would be understood readily by a skilled artisan who was already aware of the description of numerous examples of such compounds in prior art (see the 9/6/2007 dated Amendment).

There is nothing in law that that says that a class of compounds cannot be described by shared functional properties. Indeed the *Rochester* court decision cited in the Office Communication makes it very clear that it was the specific state of the art (a lack of *any* known members of the class), not the use of functional language *per se*, that caused the finding of inadequate written description. A compound defined as a compound that specifically inhibits Hh/Smo signaling is understood clearly by a person skilled in art. This functional definition is adequate for him/her to know whether a given compound would fall within or out of the defined category of compounds, particularly since numerous compounds having different structural features and acting on different components of Hh/Smo signaling had been described in prior art to inhibit Hh/Smo signaling specifically. For example, the scientific publications cited on page 3, lines 5,6 of specification had shown that cyclopamine or jervine could be used to specifically inhibit Hh/Smo signaling (see *Cooper MK et al Science* 1998;280:1603-1607, Abstract, “...these compounds specifically block the Sonic hedgehog (*Shh*) signaling pathway”; *Incardona JP et al, Development* 1998;125:3553-3562 Abstract, “cyclopamine-induced teratogenesis is due to a direct antagonism of *Shh* signal transduction”).

Withdrawal of the written description rejection and allowance of application is requested in consideration of the aforementioned facts and explanations.

IV. New Claims

New claims 41-44 are submitted herewith. Independent claim 41 recites a step of "determining that Hedgehog/Smoothed signaling is utilized for inhibition of apoptosis of the tumor cells." The skilled person is certainly able to do this either by reading or by their own investigations taken in light of the present disclosure. The remaining recitations of the new claims have been presented in other already pending claims.

V. Conclusion

The application appears to be in condition for allowance. Early and favorable action thereon is requested.

Respectfully submitted,
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Appendices

- A - Extracts from *Beachy '970*
- B - Extracts from *Lamb et al*

Enclosures

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